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1.	Your reference	46B31.GB01/
2.	Patent application number *(The Patent Office will fill in this part)*	0327775.3 — 1 DEC 2003
3.	Full name, address and postcode of the or of each applicant *(underline all surnames)*	Cambridge University Technical Services Limited The Old Schools Trinity Lane Cambridge CB2 1TS United Kingdom
	Patents ADP number *(if you know it)*	6956809004
	If the applicant is a corporate body, give the country/state of incorporation	United Kingdom
4.	Title of the invention	Anti-Inflammatory Agents
5.	Full name, address and postcode in the United Kingdom to which all correspondence relating to this form and translation should be sent	Reddie & Grose 16 Theobalds Road LONDON WC1X 8PL
	Patents ADP number *(if you know it)*	91001
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Date 1 December 200

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Anti-Inflammatory Agents

The invention relates to the use of 3-aminocaprolactam derivatives for preparing a medicament intended to prevent or treat inflammatory disorders.

Inflammation is an important component of physiological host defence. Increasingly, however, it is clear that temporally or spatially inappropriate inflammatory responses play a part in a wide range of diseases, including those with an obvious leukocyte component (such as autoimmune diseases, asthma or atherosclerosis) but also in diseases that have not traditionally been considered to involve leukocytes (such as osteoporosis or Alzheimer's disease).

The chemokines are a large family of signalling molecules with homology to interleukin-8 which have been implicated in regulating leukocyte trafficking both in physiological and pathological conditions. With more than fifty ligands and twenty receptors involved in chemokine signalling, the system has the requisite information density to address leukocytes through the complex immune regulatory processes from the bone marrow, to the periphery, then back through secondary lymphoid organs. However, this complexity of the chemokine system has at first hindered pharmacological approaches to modulating inflammatory responses through chemokine receptor blockade. It has proved difficult to determine which chemokine receptor(s) should be inhibited to produce therapeutic benefit in a given inflammatory disease.

More recently, a family of agents which block signalling by a wide range of chemokines simultaneously has been described: Reckless et al., Biochem J. (1999) 340:803-811. The first such agent, a peptide termed "Peptide 3", was found to inhibit leukocyte migration induced by 5 different chemokines, while leaving migration in response to other chemoattractants (such as fMLP or TGF-beta) unaltered. This peptide, and its analogs such as NR58-3.14.3 (i.e. Sequence ID No.1 c(DCys-DGln-DIle-DTrp-DLys-DGln-DLys-DPro-DAsp-DLeu-DCys)-NH_2), are collectively termed "Broad Spectrum Chemokine Inhibitors" (BSCIs). Grainger et al., Biochem. Pharm. 65 (2003) 1027-1034 have subsequently shown BSCIs to have potentially useful anti-inflammatory activity in a range of animal models of diseases. Interestingly, simultaneous blockade of multiple chemokines is not apparently associated with acute or chronic toxicity, suggesting this approach may be a useful strategy for developing new anti-inflammatory medications with similar benefits to steroids but with reduced side-effects.

However, peptides and peptoid derivatives such as NR58-3.14.3, may not be optimal for use in vivo. They are quite expensive to synthesise and have relatively unfavourable pharmacokinetic and pharmacodynamic properties. For example, NR58-3.14.3 is not orally bioavailable and is cleared from blood plasma with a half-life period of less than 30 minutes after intravenous injection.

Two parallel strategies have been adopted to identify novel preparations which retain the anti-inflammatory properties of peptide 3 and NR58-3.14.3, but have improved characteristics for use as pharmaceuticals. Firstly, a series of peptide analogs have been developed, some of which have longer plasma half-lives than NR58-3.14.3 and which are considerably cheaper to synthesise. Secondly, a detailed structure: activity analysis of the peptides has been carried out to identify the key pharmacophores and design small non-peptidic structures which retain the beneficial properties of the original peptide.

This second approach yielded several structurally distinct series of compounds which retained the anti-inflammatory properties of the peptides, including 16-amino and 16-aminoalkyl derivatives of the alkaloid yohimbine, as well as a range of N-substituted 3-aminoglutarimides. (Reference: Fox et al., J Med Chem 45(2002) 360-370: WO 99/12968 and WO 00/42071.) All of these compounds are broad-spectrum chemokine inhibitors which retain selectivity over non-chemokine chemoattractants, and a number of them have been shown to block acute inflammation in vivo.

The most potent and selective of these compounds was (S)-3-(undec-10-enoyl)-aminoglutarimide (NR58,4), which inhibited chemokine-induced migration in vitro with an ED_{50} of 5nM. However, further studies revealed that the aminoglutarimide ring was susceptible to enzymatic ring opening in serum. Consequently, for some applications (for example, where the inflammation under treatment is chronic, such as in autoimmune diseases) these compounds may not have optimal properties, and a more stable compound with similar anti-inflammatory properties may be superior.

As an approach to identifying such stable anlogs, various derivatives of (S)- 3-(undec-10-enoyl)-aminoglutarimide have been tested for their stability in serum. One such derivative, the 6-deoxo analog (S)-3-(undec-10-enoyl)-tetrahydropyridin-2-one, is completely stable in human serum for at least 7 days at 37°C, but has considerably reduced potency compared with the parental molecule.

Amide derivatives of 3-aminocaprolactam have already been disclosed in the art. For example:

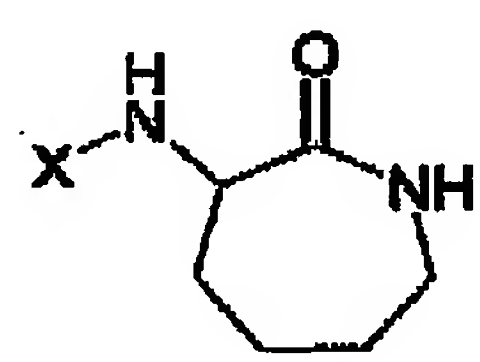
- Japanese patent application No. 09087331 describes 3-aminocaprolactam amide derivatives wherein the amide alkyl side chain may contain from 2 to 30 carbon atoms. These compounds have been presented as oil-gelating agents.

- US patent No. 6,395,282 describes immunogenic <u>conjugates</u> comprising a carrier molecule coupled to an autoinducer of a Gram negative bacteria, wherein said autoinducer can be a 3-aminocaprolactam amide derivative wherein the amide alkyl side chain may contain up to 34 carbon atoms. However, a therapeutic use is disclosed only for the <u>conjugates</u> and not for the <u>isolated</u> amide derivative.

- An article by Weiss et al. (*Research Communications in Psychology, Psychiatry and Behavior* (1992), 17(3-4), 153-159) discloses a series of 3-aminocaprolactam amide derivatives, and among others 3-hexanamido-DL-ε-caprolactam and 3-dodecanamido-DL-ε-caprolactam. These compounds are presented as having only an *in vitro* activity but no significant *in vivo* effect.

In other words, though some alkyl amide derivatives of 3-aminocaprolactam have certainly been known in the art, no actual pharmaceutical use has been described for 3-aminocaprolactam amide derivatives.

The invention provides the use of a compound of general formula (I), or a pharmaceutically acceptable salt thereof, for the preparation of a medicament intended to treat inflammatory disorder:



(I)

wherein

X is $-CO-R^1$ or $-SO_2-R^2$,

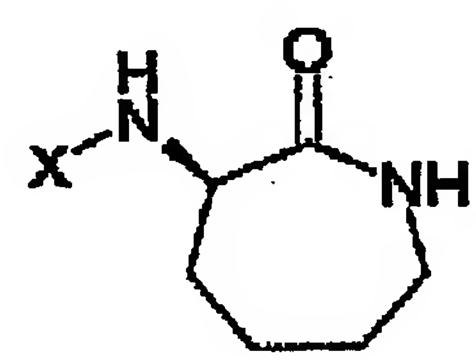
R^1 is an alkyl, haloalkyl, alkoxy, haloalkoxy, alkenyl, alkynyl or alkylamino radical of 4 to 20 carbon atoms (for example of 5 to 20 carbon atoms, of 8 to 20 carbon atoms, of 9 to 20 carbon atoms, of 10 to 18 carbon atoms, of 12 to 18 carbon atoms, of 13 to 18 carbon atoms, of 14 to 18 carbon atoms, of 13 to 17 carbon atoms.); and

R^2 is an alkyl radical of 4 to 20 carbon atoms (for example of 5 to 20 carbon atoms, of 8 to 20 carbon atoms, of 9 to 20 carbon atoms, of 10 to 18 carbon atoms, of 12 to 18 carbon atoms, of 13 to 18 carbon atoms, of 14 to 18 carbon atoms, and of 13 to 17 carbon atoms).

Alternatively R^1 and R^2 may be selected independently from a peptido radical, for example having from 1 to 4 peptidic moieties linked together by peptide bonds (for example a peptido radical of 1 to 4 amino acid residues).

The carbon atom at position 3 of the caprolactam ring is asymmetric and consequently, the compounds according to the present invention have two possible enantiomeric forms, that is, the "R" and "S" configurations. The present invention encompasses the two enantiomeric forms and all combinations of these forms, including the racemic "RS" mixtures. With a view to simplicity, when no specific configuration is shown in the structural formulae, it should be understood that the two enantiomeric forms and their mixtures are represented.

Preferably, the compounds of general formula (I) or pharmaceutically acceptable salts thereof used according to this aspect of the invention will be compounds of general formula (I')

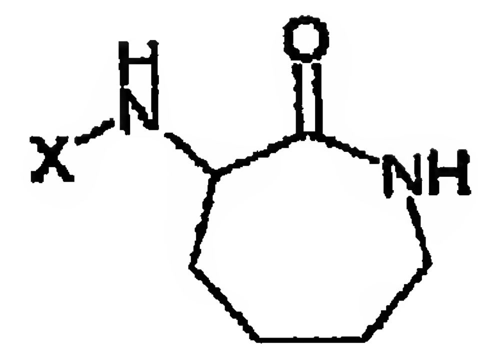


(I')

wherein X has the same meaning as above.

Preferably, the compounds of general formula (I) or (I'), or their pharmaceutically acceptable salts, will be such that the alkyl, haloalkyl, alkoxy, haloalkoxy, alkenyl, alkynyl or alkylamino part of the R^1 radical is either linear or is branched but contains a linear chain of at least 8 or 10 carbon atoms.

The invention also provides pharmaceutical compositions comprising, as active ingredient, a compound of general formula (I), or a pharmaceutically acceptable salt thereof, and at least one pharmaceutically acceptable excipient and/or carrier:



(I)

wherein

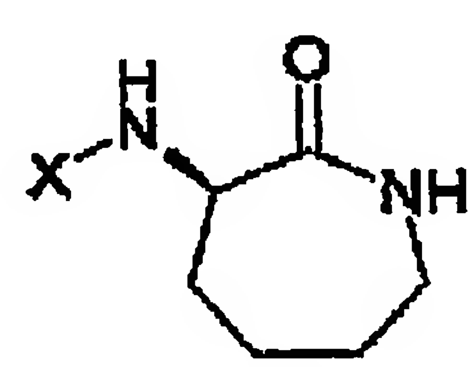
X is $-CO-R^1$ or $-SO_2-R^2$,

R^1 is an alkyl, haloalkyl, alkoxy, haloalkoxy, alkenyl, alkynyl or alkylamino radical of 4 to 20 carbon atoms (for example of 5 to 20 carbon atoms, of 8 to 20 carbon atoms, of 9 to 20 carbon atoms, of 10 to 18 carbon atoms, of 12 to 18 carbon atoms, of 13 to 18 carbon atoms, of 14 to 18 carbon atoms, of 13 to 17 carbon atoms.); and

R^2 is an alkyl radical of 4 to 20 carbon atoms (for example of 5 to 20 carbon atoms, of 8 to 20 carbon atoms, of 9 to 20 carbon atoms, of 10 to 18 carbon atoms, of 12 to 18 carbon atoms, of 13 to 18 carbon atoms, of 14 to 18 carbon atoms, and of 13 to 17 carbon atoms).

Alternatively R^1 and R^2 may be selected independently from a peptido radical, for example having from 1 to 4 peptidic moieties linked together by peptide bonds (for example a peptido radical of 1 to 4 amino acid residues).

Preferably, the compounds of general formula (I) or pharmaceutically acceptable salts thereof used according to this aspect of the invention will be compounds of general formula (I')



(I')

wherein X has the same meaning as above.

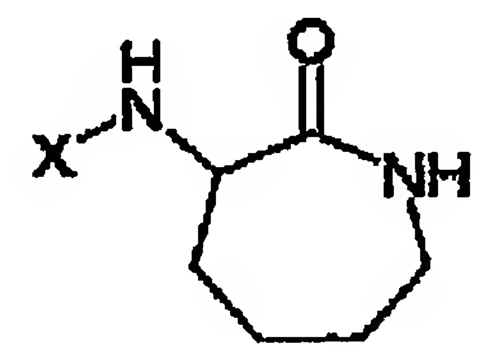
By pharmaceutically acceptable salt is meant in particular the addition salts of inorganic acids such as hydrochloride, hydrobromide, hydroiodide, sulphate, phosphate, diphosphate and nitrate or of organic acids such as acetate, maleate, fumarate, tartrate,

succinate, citrate, lactate, methanesulphonate, p-toluenesulphonate, palmoate and stearate. Also within the scope of the present invention, when they can be used, are the salts formed from bases such as sodium or potassium hydroxide. For other examples of pharmaceutically acceptable salts, reference can be made to "Salt selection for basic drugs", *Int. J. Pharm.* (1986), 33, 201-217.

The pharmaceutical composition can be in the form of a solid, for example powders, granules, tablets, gelatin capsules, liposomes or suppositories. Appropriate solid supports can be, for example, calcium phosphate, magnesium stearate, talc, sugars, lactose, dextrin, starch, gelatin, cellulose, methyl cellulose, sodium carboxymethyl cellulose, polyvinylpyrrolidine and wax. Other appropriate pharmaceutically acceptable excipients and/or carriers will be known to those skilled in the art.

The pharmaceutical compositions according to the invention can also be presented in liquid form, for example, solutions, emulsions, suspensions or syrups. Appropriate liquid supports can be, for example, water, organic solvents such as glycerol or glycols, as well as their mixtures, in varying proportions, in water.

The invention also provides compounds and salts thereof of general formula (I)



(I)

wherein

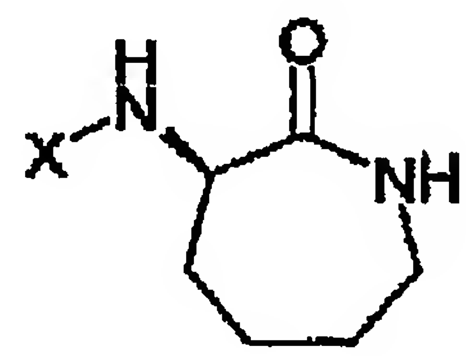
X is -CO-R^1 or -SO_2-R^2,

R^1 is an alkyl, haloalkyl, alkoxy, haloalkoxy, alkenyl, alkynyl or alkylamino radical of 4 to 20 carbon atoms (for example of 5 to 20 carbon atoms, of 8 to 20 carbon atoms, of 9 to 20 carbon atoms, of 10 to 18 carbon atoms, of 12 to 18 carbon atoms, of 13 to 18 carbon atoms, of 14 to 18 carbon atoms, of 13 to 17 carbon atoms.); and

R^2 is an alkyl radical of 4 to 20 carbon atoms (for example of 5 to 20 carbon atoms, of 8 to 20 carbon atoms, of 9 to 20 carbon atoms, of 10 to 18 carbon atoms, of 12 to 18 carbon atoms, of 13 to 18 carbon atoms, of 14 to 18 carbon atoms, and of 13 to 17 carbon atoms).

Alternatively R^1 and R^2 may be selected independently from a peptido radical, for example having from 1 to 4 peptidic moieties linked together by peptide bonds (for example a peptido radical of 1 to 4 amino acid residues).

Preferably, the compounds of general formula (I) or salts thereof used according to this aspect of the invention will be compounds of general formula (I')



(I')

wherein X has the same meaning as above.

Preferably, the compounds of general formula (I) or (I') when used in the invention, or their salts, will be such that the alkyl, haloalkyl, alkoxy, haloalkoxy, alkenyl, alkynyl or alkylamino part of the R^1 radical is either linear or is branched but contains a linear chain of at least 8 or 10 carbon atoms.

In particular, preferred compounds of general formula (I) or (I') and their salts according to any aspect of the present invention are selected from the group consisting of:

- (*S*)-3-hexadecanoylamino-caprolactam;
- (*S*)-3-undecanoylamino-caprolactam;
- (S)-3-(undec-10-enoyl)amino-caprolactam;
- (*S*)-3-(undec-10-ynoyl)amino-caprolactam;
- (*S*)-3-tetradecanoylamino-caprolactam;
- (*R*)-3-hexadecanoylamino-caprolactam;
- (*S*)-3-octadecanoylamino-caprolactam;
- (*S*)-(*Z*)-3-(hexadec-9-enoyl)amino-caprolactam;
- (*S*)-(*Z*)-3-(octadec-9-enoyl)amino-caprolactam;

- (*R*)-(*Z*)-3-(octadec-9-enoyl)amino-caprolactam;

- (*S*)-3-(2',2'-dimethyl-dodecanoyl)amino-caprolactam;

- (*S*)-3-(decyloxycarbonyl)amino-caprolactam;

- (*S*)-(*E*)-3-(dodec-2-enoyl)amino-caprolactam;

- (*S*)-3-(dec-9-enylaminocarbonyl)amino-caprolactam;

- (*S*)-3-(decylaminocarbonyl)amino-caprolactam;

and the salts thereof.

The most preferred compounds will be selected from the group consisting of: (*S*)-3-hexadecanoylamino-caprolactam (i.e. the compound of general formula (I') wherein R^1 is hexadecanyl), (S)-3-(2',2'-dimethyl-dodecanoyl)amino-caprolactam and salts thereof.

As mentioned in the discussion of prior art above, certain alkyl amide derivatives of 3-amino caprolactam may be known as compounds per se (though it is not presently known that <u>any</u> have been described as such as pharmaceutical compositions or for medical use in an anti-inflammatory context). There may be in the prior art disclosure of straight chain alkyl amide derivatives of 3-amino caprolactam. In so far as any compound in known as such, this compound is not intended to be a compound claimed per se in this invention, and is hereby disclaimed. Consequently the applicant explicitly distinguishes herein between straight chain alkyl derivatives covered by the definition of formula (I) and (I') herein, and branched chain alkyl derivatives of formula (I) and (I') herein. The definition of R^1 used herein in connection with compounds per se may included all alkyl derivatives; alternatively R^1 may include all alkyl derivatives with the exception of certain specified straight chain alkyl derivatives; alternatively R^1 may include all branched chain alkyl derivatives; and as a further alternative the definition of R^1 may exclude all alkyl amide derivatives of 3-amino caprolactam.

The invention includes compounds, compositions and uses thereof as defined, wherein the compound is in hydrated or solvated form.

As indicated in the Introduction, certain alkyl aminocaprolcactam compounds per se, and compositions/conjugates containing them, may already be known in the prior art. Any such known compounds or compositions will be disclaimed from the present

invention, either by specific disclaimer or by generic disclaimer of a class of compounds/compositions.

The amide derivatives of 3-aminocaprolactam described here BSCIs. They are relatively inexpensive to synthesise, using facile synthesis routes provided herein; they are stable in human serum and consequently have excellent pharmacokinetic properties; they are orally bioavailable; they are highly potent broad-spectrum chemokine inhibitors in vitro with excellent selectivity over non-chemokine chemoattractants; they are highly potent and effective anti-inflammatory agents in vivo in rodent models of inflammation; their administration is not associated with any significant acute toxicity at the doses necessary to achieve a maximal therapeutic effect. Taken together, these properties suggest that amide derivatives of 3-aminocaprolactam represent, anti-inflammatory medications with advantages over previously described compounds.

In comparison to the prior art the improvement of the present invention lies in the introduction of the aminocaprolactam moiety. The nature of the side chain (whether alkyl amide, alkyl sulfonamide, or peptido) modulates the properties (for example by changing solubility and pharmacodynamics) but it does not affect the core bioactivity of the molecule.

Prior art peptides (such as NR58-3.14.3) have the disadvantages that: (a) they are expensive and require solid phase synthesis (at least for the longer ones) and (b) they clear very quickly via the kidneys and (c) they are generally less potent.

The prior art aminoglutarimides are cheap, not cleared quickly via the kidneys and more potent BUT they do not show metabolic stability.

The improvement described here, the aminocaprolactams, are cheap, not cleared by the kidney and even more potent, and are also metabolically stable.

According to this invention, inflammatory disorders intended to be prevented or treated by the compounds of general formula (I) or (I') or the pharmaceutically acceptable salts thereof or pharmaceutical compositions or medicaments containing them as active ingredients include notably:

- autoimmune diseases, for example such as multiple sclerosis;
- vascular disorders including stroke, coronary artery diseases, myocardial infarction, unstable angina pectoris, atherosclerosis or vasculitis, e. g., Behçet's syndrome, giant cell arteritis, polymyalgia rheumatica, Wegener's granulomatosis, Churg-Strauss syndrome vasculitis, Henoch-Schönlein purpura and Kawasaki disease;

- viral infection or replication, e.g. infections due to or replication of viruses including pox virus, herpes virus (e. g., Herpesvirus samiri), cytomegalovirus (CMV) or lentivirus;
- asthma;
- osteoporosis; (low bone mineral density);
- tumor growth;
- rheumatoid arthritis;
- organ transplant rejection and/or delayed graft or organ function, e.g. in renal transplant patients;
- a disorder characterised by an elevated TNF-α level;
- psoriasis;
- skin wounds;
- disorders caused by intracellular parasites such as malaria or tuberculosis;
- allergies; or
- Alzheimer's disease.

According to this invention, further inflammatory disorders include:

- ALS;
- fibrosis (particularly pulmonary fibrosis, but not limited to fibrosis in the lung);
- the formation of adhesions (particularly in the peritoneum and pelvic region).
- antigen induced recall response
- immune response suppression

These clinical indications fall under the general definition of inflammatory disorders or disorders characterized by elevated TNFα levels.

Where legally permissible, the invention also provides a method of treatment, amelioration or prophylaxis of the symptoms of an inflammatory disease (including an

adverse inflammatory reaction to any agent) by the administration to a patient of an anti-inflammatory amount of a compound, composition or medicament as claimed herein.

Administration of a medicament according to the invention can be carried out by topical, oral, parenteral route, by intramuscular injection, etc.

The administration dose envisaged for a medicament according to the invention is comprised between 0.1 mg and 10 g depending on the type of active compound used.

According to the invention, the compounds of general formula (I) or (I') can be prepared using the processes described hereafter.

Preparation of the compounds of general formula (I) or (I')

All the compounds of general formula (I') or (I') can be prepared easily according to general methods known to the person skilled in the art.

Nevertheless, the following preferred synthetic routes are proposed:

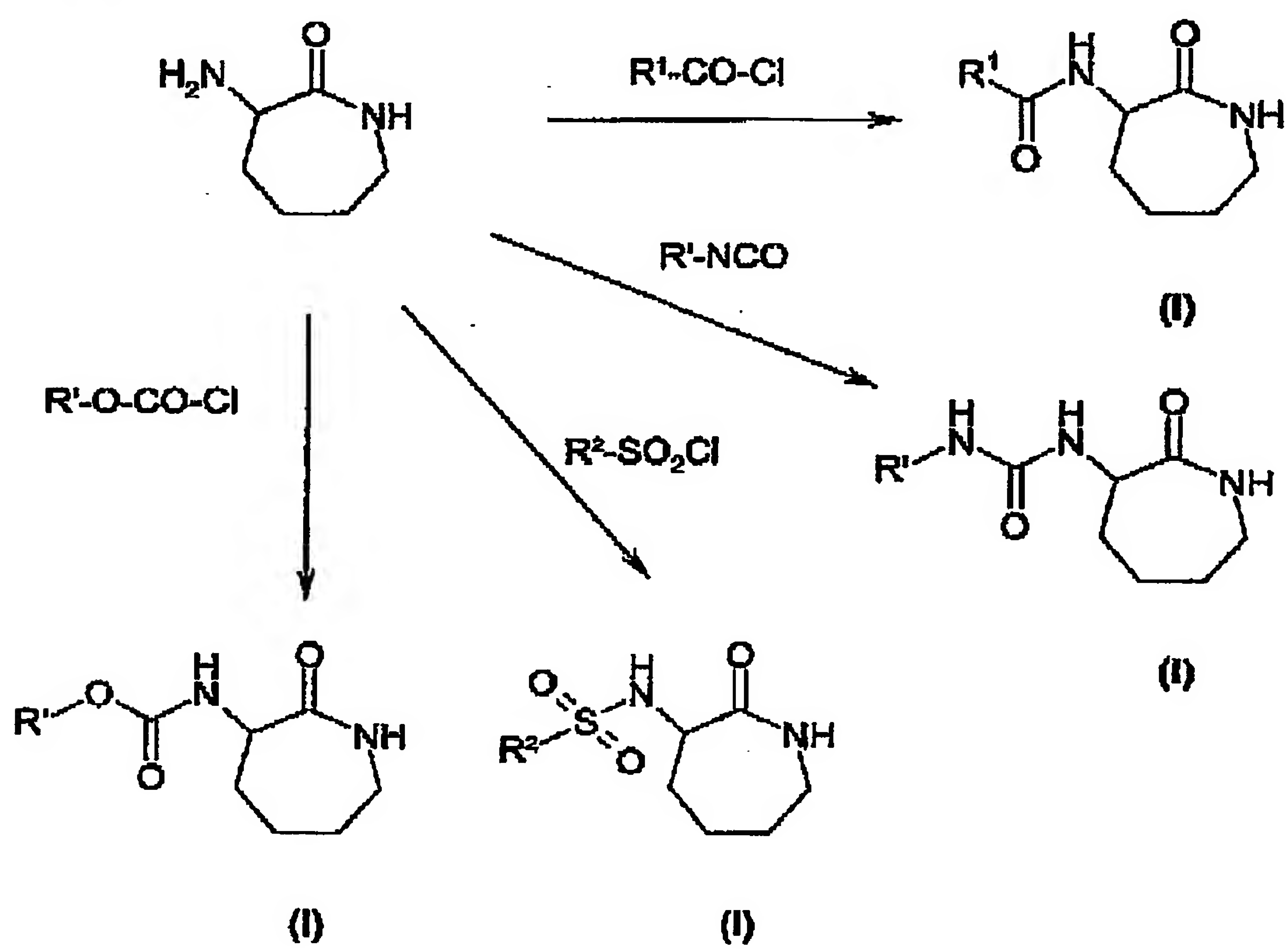


Diagram 1

According to the routes shown in Diagram 1:

- 3-amino-caprolactam is treated by an acid chloride of general formula R^1-CO-Cl wherein R^1 is an alkyl, haloalkyl, alkenyl or alkynyl radical to produce the compounds of general formula (I) wherein X is –CO-R^1 and R^1 is an alkyl, haloalkyl, alkenyl or alkynyl radical; or
- 3-amino-caprolactam is treated by an isocyanate of general formula R'-NCO wherein R' is alkyl to produce the compounds of general formula (I) wherein X is –CO-R^1 and R^1 is an alkylamino radical ;
- 3-amino-caprolactam is treated by a sulphochloride of general formula R^2-SO_2Cl wherein R^2 is alkyl to produce the compounds of general formula (I) wherein X is –SO_2-R^2 and R^2 is an alkyl radical ; or
- 3-amino-caprolactam is treated by a chloroformate of general formula R'-O-CO-Cl wherein R' is alkyl to produce the compounds of general formula (I) wherein X is –CO-R^1 and R^1 is an alkoxy radical.

The reactions shown in Diagram 1 may be carried out, for example, in chloroform or dichloromethane. The most preferred reaction solvent is dichloromethane.

The above reactions are preferably carried out in the presence of a base, for example Na_2CO_3.

All the above reactions may be carried out at ambient temperature (about 25 °C) or more generally at a temperature between 20 and 50 °C.

DEFINITIONS

The term "about" refers to an interval around the considered value. As used in this patent application, "about X" means an interval from X minus 10% of X to X plus 10% of X, and preferably an interval from X minus 5% of X to X plus 5% of X.

The use of a numerical range in this description is intended unambiguously to include within the scope of the invention all individual integers within the range and all the combinations of upper and lower limit numbers within the broadest scope of the given range. Hence, for example, the range of 4 to 20 carbon atoms specified in respect of (*inter alia*) formula I is intended to include all integers between 4 and 20 and all sub-ranges of each combination of upper and lower numbers, whether exemplified explicitly or not.

As used herein, the term "comprising" is to be read as meaning both comprising and consisting of. Consequently, where the invention relates to a "pharmaceutical composition comprising as active ingredient" a compound, this terminology is intended to cover both compositions in which other active ingredients may be present and also compositions which consist only of one active ingredient as defined.

The term "peptidic moieties" used herein is intended to include the following 20 naturally-occurring proteogenic amino acid residues:

SYMBOL	MEANING
Ala	Alanine
Cys	Cysteine
Asp	Aspartic Acid
Glu	Glutamic Acid
Phe	Phenylalanine
Gly	Glycine
His	Histidine
Ile	Isoleucine
Lys	Lysine
Leu	Leucine
Met	Methionine
Asn	Asparagine
Pro	Proline
Gln	Glutamine
Arg	Arginine
Ser	Serine
Thr	Threonine
Val	Valine
Trp	Tryptophan
Tyr	Tyrosine

Modified and unusual amino acid residues, as well as peptido-mimetics, are also intended to be encompassed within the definition of "peptidic moieties".

Unless otherwise defined, all the technical and scientific terms used here have the same meaning as that usually understood by an ordinary specialist in the field to which this invention belongs. Similarly, all the publications, patent applications, all the patents and all other references mentioned here are incorporated by way of reference (where legally permissible).

The following examples are presented in order to illustrate the above procedures and should in no way be considered to limit the scope of the invention.

FIGURES

Figure 1 provides a comparison of (R)-and (S)- enantiomers of amide derivatives of aminocaprolactam as inhibitors of MCP-1 induced migration.

EXAMPLES

General procedure for the synthesis of the starting compounds

The hydrochlorides of (*R*) and (*S*)-3-amino-caprolactam, and the hydro-pyrrolidine-5-carboxylates of (*R*,*R*) and (*S*,*S*)-3-amino-caprolactam were synthesised according to literature (cf. Boyle et al., *J. Am. Chem. Soc.* (1979), **44**, 4841-4847; Rezler et al., *J. Med. Chem.* (1997), **40**, 3508-3515).

Example 1: (*S*)-3-hexadecanoylamino-caprolactam:

(*S*)-3-amino-caprolactam hydrochloride **1** (5 mmol) and Na_2CO_3 (15 mmol) in water (25 ml) were added to a solution of hexadecanoyl chloride (5 mmol) in dichloromethane (25 ml) at ambient temperature and the reaction mixture was stirred for 2 hours. The organic layer was then separated and the aqueous phase was extracted with additional dichloromethane (2 × 25 ml). The combined organic layers were dried over Na_2CO_3 and reduced *in vacuo*. The residue was purified by recrystallisation from EtOAc to give the title compound (1.41 g; 77%).

Melting point: 99-100 °C.

$[\alpha]_D^{25}$ (c = 1, $CHCl_3$) = +32.0.

IR: ν_{max} (cm^{-1}): 3325, 3272 (NH), 1666, 1655, 1631 (CO), 1524 (NH).

^{1}H NMR (δ_H, 500 MHz, $CDCl_3$): 6.88 (1H, d, *J* 5.5, CHN*H*), 6.72 (1H, br s, CH_2NH), 4.49 (1H, ddd, *J* 11, 6, 1, C*H*NH), 3.29-3.16 (2H, m, CH_2NH), 2.17 (2H, t, *J* 7.5, CH_2CONH), 2.03 (1H, br d, *J* 13.5, ring CH), 1.98-1.89 (1H, m, ring CH), 1.85-1.73 (2H, m, ring CH), 1.58 (2H, br qn *J* 7.0, CH_2CH_2CONH), 1.43 (1H, br qd, *J* 14, 3, ring CH), 1.38-1.29 (1H, br m, ring CH), 1.29-1.14 (24H, m, $(CH_2)_{12}$) and 0.83 (3H, t, *J* 6.5, CH_3).

^{13}C NMR (δ_C, 125 MHz, $CDCl_3$): 175.9, 172.3 (CO), 52.0 (NHCHCO), 42.1 (NCH_2), 36.6, 31.9, 31.7, 29.6 (×6), 29.4, 29.3 (×2), 29.2, 28.8, 27.9, 25.6, 22.6 (CH_2) and 14.1 (CH_3).

m/z ($C_{22}H_{42}N_2O_2Na$): 389.31450 (calculated: 389.3144).

__Example 2:__ **(*S*)-3-undecanoylamino-caprolactam:**

(*S*)-3-amino-caprolactam hydrochloride (2 mmol) and Na_2CO_3 (6 mmol) in water (25 ml) were added to a solution of undecanoyl chloride (2 mmol) in dichloromethane (25 ml) at ambient temperature and the reaction mixture was stirred for 2 hours. The organic layer was then separated and the aqueous phase was extracted with additional dichloromethane (2 × 25 ml). The combined organic layers were dried over Na_2CO_3 and reduced *in vacuo*. The residue was purified by recrystallisation from EtOAc to give the title compound (397 mg, 67%).

Melting point: 91-92 °C.

$[\alpha]_D^{22}$ (c = 1, $CHCl_3$) = +30.2.

IR: ν_{max} (cm^{-1}): 3342, 3313 (NH), 1676, 1638 (CO), 1519 (NH); 3342, 3292 (NH), 1671, 1639 (CO), 1513 (NH).

^{1}H NMR (δ_H, 500 MHz, d_6-DMSO): 7.76 (1H, t, *J* 6, CH_2NH), 7.68 (1H, d, *J* 7, CHN*H*), 4.38 (1H, dd, *J* 10, 7, C*H*NH), 3.15 (1H, ddd, *J* 15.5, 11, 5, C*H*HNH), 3.04 (1H, dt, *J* 13, 6, CH*H*NH), 2.19-2.06 (2H, m, CH_2CONH), 1.85 (1H, dt, *J* 10.5, 3, C-5 H), 1.77-1.68 (2H, m, C-4 H, C-6 H), 1.60 (1H, qt, *J* 12, 3.5, C-5 H), 1.46 (2H, br qn *J* 6.5, CH_2CH_2CONH), 1.35 (1H, qd, *J* 12.5, 3, C-4 H), 1.31-1.13 (15H, m, $(CH_2)_7$ + C-6 H) and 0.85 (3H, t, *J* 7.0, CH_3).

^{13}C NMR (δ_C, 125 MHz, d_6-DMSO): 174.4 (CO-ring), 171.3 (CO-chain), 51.3 (NH*C*HCO), 40.7 (NCH_2), 35.2, 31.4, 31.3, 29.1, 29.0 (×2), 28.9, 28.8, 28.7, 27.8, 25.4, 22.2 (CH_2) and 14.0 (CH_3).

m/z ($C_{17}H_{32}N_2O_2Na$): 319.23540 (calculated: 319.2361).

Example 3: **(S)-3-(undec-10-enoyl)amino-caprolactam:**

(*S*)-3-amino-caprolactam hydrochloride (2 mmol) and Na_2CO_3 (6 mmol) in water (25 ml) were added to a solution of undec-10-enoyl chloride (2 mmol) in dichloromethane (25 ml) at ambient temperature and the reaction mixture was stirred for 2 hours. The organic layer was then separated and the aqueous phase was extracted with additional dichloromethane (2 × 25 ml). The combined organic layers were dried over Na_2CO_3 and reduced *in vacuo*. The residue was purified by recrystallisation from EtOAc to give the title compound (423 mg; 72%).

Melting point: 83-84 °C.

$[\alpha]_D^{25}$ (c = 1, $CHCl_3$) = +40.1.

IR: ν_{max} (cm^{-1}): 3327, 3273 (NH), 1655, 1630 (CO), 1521 (NH).

^{1}H NMR (δ_H, 500 MHz, d_6-DMSO): 7.75 (1H, t, *J* 6, CH_2NH), 7.66 (1H, d, *J* 7, CHN*H*), 5.76 (1H, ddt, *J* 17, 10, 6.5 CH_2=C*H*), 4.96 (1H, dq, *J* 17, 2, C*H*H=CH), 4.96 (1H, ddt, *J* 17, 2, 1, C*H*H=CH), 4.36 (1H, dd, *J* 10, 7, C*H*NH), 3.14 (1H, ddd, *J* 15.5, 11.5, 5, C*H*HNH), 3.03 (1H, br dt, *J* 13, 5.5, CH*H*NH), 2.16-2.06 (2H, m, CH_2CONH), 1.98 (2H, br q, *J* 7, CH_2=CHCH_2), 1.85 (1H, dt, *J* 10.5, 3, C-5 H), 1.75-1.67 (2H, m, C-4 H, C-6 H), 1.60 (1H, qt, *J* 13, 3.5, C-5 H), 1.44 (2H, br qn, *J* 7, CH_2CH_2CONH), 1.39-1.27 (3H, m, CH_2=CHCH_2CH_2 + C-4 H) and 1.31-1.13 (9H, m, $(CH_2)_4$ + C-6 H).

^{13}C NMR (δ_C, 125 MHz, d_6-DMSO): 174.4 (CO-ring), 171.3 (CO-chain), 138.9 (CH_2=CH), 114.7 (CH_2=CH), 51.3 (NHCHCO), 40.7 (NCH_2), 35.3, 33.3, 31.3, 29.0, 28.9 (×2) 28.7, 28.6, 28.4, 27.8 and 25.4 (CH_2).

m/z ($C_{17}H_{30}N_2O_2Na$): 317.21970 (calculated: 317.2205).

Example 4: **(*S*)-3-(undec-10-ynoyl)amino-caprolactam:**

(*S*)-3-amino-caprolactam hydrochloride (2 mmol) and Na_2CO_3 (6 mmol) in water (25 ml) were added to a solution of undec-10-ynoyl chloride (2 mmol) in dichloromethane (25 ml) at ambient temperature and the reaction mixture was stirred for 2 hours. The organic layer was then separated and the aqueous phase was extracted with additional dichloromethane (2 × 25 ml). The combined organic layers were dried

over Na_2CO_3 and reduced *in vacuo*. The residue was purified by recrystallisation from EtOAc to give the title compound (362 mg; 62%).

Melting point: 73-75 °C.

$[\alpha]_D^{22}$ (c = 1, $CHCl_3$) = +42.1.

IR: ν_{max} (cm^{-1}): 3332, 3295 (NH), 1667, 1633 (CO), 1523 (NH).

^1H NMR (δ_H, 500 MHz, d_6-DMSO): 7.76 (1H, t, *J* 5.5, $CH_2N\mathit{H}$), 7.68 (1H, d, *J* 7, $CHN\mathit{H}$), 4.36 (1H, dd, *J* 11, 7, $C\mathit{H}NH$), 3.16 (1H, ddd, *J* 15.5, 11.5, 5, $C\mathit{H}HNH$), 3.03 (1H, br dt, *J* 14, 7, $CH\mathit{H}NH$), 2.17-2.07 (4H, m, $C\mathit{H}_2CONH$ + $C\mathit{H}_2CCH$), 1.85 (1H, m, C-5 H), 1.77-1.67 (2H, m, C-4 H, C-6 H), 1.62 (1H, br qt, *J* 13, 3.0, C-5 H), 1.50-1.28 (5H, m, $C\mathit{H}_2CH_2CONH$ + $HCCCH_2C\mathit{H}_2$ + C-4 H) and 1.28-1.13 (9H, m, $(CH_2)_4$ + C-6 H).

^{13}C NMR (δ_C, 125 MHz, d_6-DMSO): 174.4 (CO-ring), 171.3 (CO-chain), 84.6 (CH_2CCH), 71.1 ($CH_2C\mathit{C}H$), 51.3 ($NH\mathit{C}HCO$), 40.7 (NCH_2), 35.2, 31.3, 29.0, 28.8, 28.7, 28.5, 28.2, 28.0, 27.8, 25.4 and 17.8 (CH_2).

m/z ($C_{17}H_{28}N_2O_2Na$): 317.20470 (calculated: 315.2048).

Example 5: ***(S)*-3-dodecanoylamino-caprolactam:**

(*S*)-3-amino-caprolactam hydrochloride (2 mmol) and Na_2CO_3 (6 mmol) in water (25 ml) were added to a solution of dodecanoyl chloride (2 mmol) in dichloromethane (25 ml) at ambient temperature and the reaction mixture was stirred for 2 hours. The organic layer was then separated and the aqueous phase was extracted with additional dichloromethane (2 × 25 ml). The combined organic layers were dried over Na_2CO_3 and reduced *in vacuo*. The residue was purified by recrystallisation from EtOAc to give the title compound (439 mg, 71%).

Melting point: 93-94 °C.

$[\alpha]_D^{25}$ (c = 1, $CHCl_3$) = +35.5.

IR: ν_{max} (cm^{-1}): 3324, 3267 (NH), 1666, 1630 (CO), 1521 (NH).

^1H NMR (δ_H, 500 MHz, d_6-DMSO): 7.76 (1H, br s, $CH_2N\mathit{H}$), 7.67 (1H, d, *J* 7, $CHN\mathit{H}$), 4.38 (1H, dd, *J* 10.5, 7.5, $C\mathit{H}NH$), 3.15 (1H, ddd, *J* 15.5, 11.5, 5, $C\mathit{H}HNH$), 3.05 (1H, dt, *J* 14.5, 5.5, $CH\mathit{H}NH$), 2.17-2.07 (2H, m, $C\mathit{H}_2CONH$), 1.90-1.80 (1H, m, C-5 H), 1.77-1.68 (2H, m, C-4 H, C-6 H), 1.62 (1H, br qt, *J* 12, 3.5, C-5 H), 1.46 (2H, br qn *J*

6.0, CH_2CH_2CONH), 1.36 (1H, qd, *J* 12.5, 2.5, C-4 H), 1.31-1.13 (17H, m, $(CH_2)_8$ + C-6 H) and 0.85 (3H, t, *J* 6.5, CH_3).

^{13}C NMR (δ_C, 125 MHz, d_6-DMSO): 174.4 (CO-ring), 171.2 (CO-chain), 51.3 (NHCHCO), 40.7 (NCH_2), 35.3, 31.4, 31.3, 29.1 (×3), 29.0 (×2), 28.8, 28.7, 27.8, 25.4, 22.2 (CH_2) and 14.0 (CH_3).

m/z ($C_{18}H_{34}N_2O_2Na$): 333.25150 (calculated: 333.2518).

__Example 6:__ **(*S*)-3-tetradecanoylamino-caprolactam:**

(*S*)-3-amino-caprolactam hydrochloride (2 mmol) and Na_2CO_3 (6 mmol) in water (25 ml) were added to a solution of tetradecanoyl chloride (2 mmol) in dichloromethane (25 ml) at ambient temperature and the reaction mixture was stirred for 2 hours. The organic layer was then separated and the aqueous phase was extracted with additional dichloromethane (2 × 25 ml). The combined organic layers were dried over Na_2CO_3 and reduced *in vacuo*. The residue was purified by recrystallisation from EtOAc to give the title compound (412 mg; 61%).

Melting point: 97-98 °C.

$[\alpha]_D^{25}$ (c = 1, $CHCl_3$) = +33.2.

IR: ν_{max} (cm^{-1}): 3326, 3273 (NH), 1666, 1655, 1631 (CO), 1523 (NH).

^1H NMR (δ_H, 500 MHz, $CDCl_3$): 6.87 (1H, d, *J* 5.5, CHN*H*), 6.66-6.48 (1H, br m, CH_2NH), 4.50 (1H, dd, *J* 11, 6, C*H*NH), 3.30-3.16 (2H, m, CH_2NH), 2.18 (2H, t, *J* 7.5, CH_2CONH), 2.04 (1H, br d, *J* 13.5, ring CH), 2.00-1.92 (1H, m, ring CH), 1.86-1.74 (2H, m, ring CH), 1.59 (2H, br qn *J* 7.0, CH_2CH_2CONH), 1.43 (1H, br q, *J* 12.5, ring CH), 1.31 (1H, br q, *J* 13, ring CH), 1.31-1.13 (20H, m, $(CH_2)_{10}$) and 0.85 (3H, t, *J* 6.5, CH_3).

^{13}C NMR (δ_C, 125 MHz, $CDCl_3$): 175.9, 172.3 (CO), 52.0 (NHCHCO), 42.1 (NCH_2), 36.6, 31.9, 31.7, 29.6 (×4), 29.4, 29.3 (×2), 29.2, 28.8, 27.9, 25.6, 22.6 (CH_2) and 14.1 (CH_3).

m/z ($C_{20}H_{38}N_2O_2Na$): 361.28270 (calculated: 361.2831).

__Example 7:__ **(*R*)-3-hexadecanoylamino-caprolactam:**

(*R,R*)-3-amino-caprolactam hydro-pyrrolidine-5-carboxylate (5 mmol) and Na_2CO_3 (15 mmol) in water (25 ml) were added to a solution of hexadecanoyl chloride (5 mmol)

in dichloromethane (25 ml) at ambient temperature and the reaction mixture was stirred for 2 hours. The organic layer was then separated and the aqueous phase was extracted with additional dichloromethane (2 × 25 ml). The combined organic layers were dried over Na_2CO_3 and reduced *in vacuo*. The residue was purified by recrystallisation from EtOAc to give the title compound (1.23 g; 67%).

Melting point: 99-100 °C.

$[\alpha]_D^{25}$ (c = 1, $CHCl_3$) = -32.0.

<u>Example 8:</u> (*S*)-3-octadecanoylamino-caprolactam:

(*S*)-3-amino-caprolactam hydrochloride (2 mmol) and Na_2CO_3 (6 mmol) in water (25 ml) were added to a solution of octadecanoyl chloride (2 mmol) in dichloromethane (25 ml) at ambient temperature and the reaction mixture was stirred for 2 hours. The organic layer was then separated and the aqueous phase was extracted with additional dichloromethane (2 × 25 ml). The combined organic layers were dried over Na_2CO_3 and reduced *in vacuo*. The residue was purified by recrystallisation from EtOAc to give the title compound (648 mg; 82%).

Melting point: 87-88 °C.

$[\alpha]_D^{25}$ (c = 1, $CHCl_3$) = +31.9.

IR: ν_{max} (cm^{-1}): 3327, 3272 (NH), 1667, 1655, 1631 (CO), 1524 (NH).

^{1}H NMR (δ_H, 500 MHz, $CDCl_3$): 6.88 (1H, d, *J* 5.5, CHN*H*), 6.72-6.58 (1H, br m, CH_2N*H*), 4.50 (1H, dd, *J* 11, 6, C*H*NH), 3.29-3.16 (2H, m, C*H*$_2$NH), 2.17 (2H, t, *J* 7.5, C*H*$_2$CONH), 2.03 (1H, br d, *J* 13, ring CH), 1.99-1.90 (1H, m, ring CH), 1.86-1.73 (2H, m, ring CH), 1.58 (2H, br qn *J* 7.0, C*H*$_2$$CH_2$CONH), 1.42 (1H, br qd, *J* 14, 3, ring CH), 1.38-1.30 (1H, br m, ring CH), 1.30-1.14 (28H, m, $(CH_2)_{14}$) and 0.84 (3H, t, *J* 6.5, CH_3).

^{13}C NMR (δ_C, 125 MHz, $CDCl_3$): 175.9, 172.3 (CO), 52.0 (NHCHCO), 42.1 (NCH_2), 36.6, 31.9, 31.7, 29.6 (×8), 29.4, 29.3 (×2), 29.2, 28.8, 27.9, 25.6, 22.6 (CH_2) and 14.1 (CH_3).

m/z ($C_{24}H_{46}N_2O_2Na$): 417.34460 (calculated: 417.3457).

<u>Example 9:</u> (*S*)-(*Z*)-3-(hexadec-9-enoyl)amino-caprolactam:

(*S*,*S*)-3-amino-caprolactam hydro-pyrrolidine-5-carboxylate 2 (2 mmol) and Na_2CO_3 (6 mmol) in water (25 ml) were added to a solution of (*Z*)-hexadec-9-enoyl chloride (2 mmol) in dichloromethane (25 ml) at ambient temperature and the reaction mixture was stirred for 2 hours. The organic layer was then separated and the aqueous phase was extracted with additional dichloromethane (2 × 25 ml). The combined organic layers were dried over Na_2CO_3 and reduced *in vacuo*. The residue was purified by silica column chromatography (eluent: EtOAc to 9:1 EtOAc:MeOH) to give the title compound (406 mg; 56%).

Melting point: 67-68 °C.

$[\alpha]_D^{25}$ (c = 1, $CHCl_3$) = +33.2.

IR: ν_{max} (cm^{-1}): 3324, 3268 (NH), 1655, 1630 (CO), 1524 (NH).

^{1}H NMR (δ_H, 500 MHz, $CDCl_3$): 6.88 (1H, d, *J* 5.5, CHN*H*), 6.67 (1H, br s, CH_2NH), 5.33-5.25 (2H, m, C*H*=C*H*), 4.50 (1H, ddd, *J* 11, 6, 1, C*H*NH), 3.29-3.16 (2H, m, CH_2NH), 2.17 (2H, t, *J* 7.5, CH_2CONH), 2.03 (1H, br d, *J* 13, ring CH), 1.99-1.90 (5H, m, ring CH + $CH_2CH=CHCH_2$), 1.84-1.72 (2H, m, ring CH), 1.58 (2H, br qn *J* 7.0, CH_2CH_2CONH), 1.43 (1H, br qd, *J* 14, 3, ring CH), 1.38-1.30 (1H, br m, ring CH), 1.30-1.14 (16H, m, $(CH_2)_4CH_2CH=CHCH_2(CH_2)_4$) and 0.84 (3H, t, *J* 7, CH_3).

^{13}C NMR (δ_C, 125 MHz, $CDCl_3$): 175.9, 172.3 (CO), 129.8 (×2) (CH=CH), 52.0 (NHCHCO), 42.0 (NCH_2), 36.6, 31.7 (×2), 29.7 (×2), 29.2 (×2), 29.1, 29.0, 28.8, 27.9, 27.2, 27.1, 25.6, 22.6 (CH_2) and 14.1 (CH_3).

m/z ($C_{22}H_{40}N_2O_2Na$): 387.29700 (calculated: 387.2987).

Example 10: (*S*)-(*Z*)-3-(octadec-9-enoyl)amino-caprolactam:

(*S*,*S*)-3-amino-caprolactam hydro-pyrrolidine-5-carboxylate (2 mmol) and Na_2CO_3 (6 mmol) in water (25 ml) were added to a solution of (*Z*)-octadec-9-enoyl chloride (2 mmol) in dichloromethane (25 ml) at ambient temperature and the reaction mixture was stirred for 2 hours. The organic layer was then separated and the aqueous phase was extracted with additional dichloromethane (2 × 25 ml). The combined organic layers were dried over Na_2CO_3 and reduced *in vacuo*. The residue was purified by silica column chromatography (eluent: EtOAc to 9:1 EtOAc:MeOH) to give the title compound (514 mg; 66%).

Melting point: 66-67 °C.

$[\alpha]_D^{25}$ (c = 1, $CHCl_3$) = +30.9.

IR: ν_{max} (cm^{-1}): 3327, 3268 (NH), 1655, 1631 (CO), 1523 (NH).

^1H NMR (δ_H, 500 MHz, $CDCl_3$): 6.88 (1H, d, *J* 5.5, CHN*H*), 6.74 (1H, br t, *J* 5, CH_2N*H*), 5.33-5.24 (2H, m, C*H*=C*H*), 4.49 (1H, ddd, *J* 11, 6, 1.5, C*H*NH), 3.29-3.14 (2H, m, CH_2NH), 2.16 (2H, t, *J* 7.5, CH_2CONH), 2.03 (1H, br d, *J* 13.5, ring CH), 1.99-1.89 (5H, m, ring CH + CH_2CH=CHCH_2), 1.84-1.72 (2H, m, ring CH), 1.58 (2H, br qn *J* 7.0, C$H_2$$CH_2$CONH), 1.42 (1H, br qd, *J* 14, 3, ring CH), 1.38-1.30 (1H, br m, ring CH), 1.30-1.14 (20H, m, $(CH_2)_6CH_2CH{=}CHCH_2(CH_2)_4$) and 0.83 (3H, t, *J* 7, CH_3).

^{13}C NMR (δ_C, 125 MHz, $CDCl_3$): 175.9, 172.3 (CO), 129.9. 129.7 (CH=CH), 52.0 (NHCHCO), 42.0 (NCH_2), 36.6, 31.8, 31.7, 29.7 (×2), 29.5, 29.3 (×3), 29.2, 29.1, 28.8, 27.9, 27.2, 27.1, 25.6, 22.6 (CH_2) and 14.1 (CH_3).

m/z ($C_{24}H_{44}N_2O_2Na$): 415.32820 (calculated: 415.3300).

<u>Example 11:</u> (*R*)-(*Z*)-3-(octadec-9-enoyl)amino-caprolactam:

(*R*,*R*)-3-amino-caprolactam hydro-pyrrolidine-5-carboxylate 2 (2 mmol) and Na_2CO_3 (6 mmol) in water (25 ml) were added to a solution of (*Z*)-octadec-9-enoyl chloride (2 mmol) in dichloromethane (25 ml) at ambient temperature and the reaction mixture was stirred for 2 hours. The organic layer was then separated and the aqueous phase was extracted with additional dichloromethane (2 × 25 ml). The combined organic layers were dried over Na_2CO_3 and reduced *in vacuo*. The residue was purified by silica column chromatography (eluent: EtOAc to 9:1 EtOAc:MeOH) to give the title compound (574 mg; 73%).

Melting point: 66-67 °C.

$[\alpha]_D^{25}$ (c = 1, $CHCl_3$) = -31.4.

<u>Example 12:</u> (*S*)-3-(2',2'-dimethyl-dodecanoyl)amino-caprolactam:

(*S*,*S*)-3-amino-caprolactam hydro-pyrrolidine-5-carboxylate 2 (2 mmol) and Na_2CO_3 (6 mmol) in water (25 ml) were added to a solution of 2,2-dimethyl-dodecanoyl chloride (2 mmol) in dichloromethane (25 ml) at ambient temperature and the reaction mixture was stirred for 2 hours. The organic layer was then separated and the aqueous phase was extracted with additional dichloromethane (2 × 25 ml). The combined organic layers were dried over Na_2CO_3 and reduced *in vacuo*. The residue was purified by silica

column chromatography (eluent: EtOAc to 9:1 EtOAc:MeOH) to give the title compound (543 mg; 80%).

Melting point: 41-42 °C.

$[\alpha]_D^{25}$ (c = 1, $CHCl_3$) = +28.0.

IR: ν_{max} (cm^{-1}): 3403, 3265 (NH), 1673, 1641 (CO), 1497 (NH).

^{1}H NMR (δ_H, 500 MHz, $CDCl_3$): 7.08 (1H, d, *J* 5.5, CHN*H*), 6.67 (1H, br s, CH_2N*H*), 4.44 (1H, dd, *J* 11, 5.5, C*H*NH), 3.28-3.15 (2H, m, CH_2NH), 2.01 (1H, br d, *J* 13, ring CH), 1.98-1.89 (1H, m, ring CH), 1.84-1.72 (2H, m, ring CH), 1.47-1.30 (3H, br m, ring CH + CH_2CMe$_2$CONH), 1.27-1.15 (17H, br m, ring CH +$(CH_2)_8$) 1.13 (3H, s, C*Me*Me), 1.12 (3H, s, CMe*Me*) and 0.82 (3H, t, *J* 7, CH$_2$CH_3).

^{13}C NMR (δ_C, 125 MHz, $CDCl_3$): 177.1, 176.0 (CO), 52.0 (NH*C*HCO), 41.9 (*C*Me$_2$), 42.1, 41.3, 31.8, 31.5, 30.1, 29.6, 29.5 (×2), 29.3, 28.9, 27.9 (CH_2), 25.3, 25.2 (CH_3), 24.8, 22.6 (CH_2) and 14.1 (CH_3).

m/z ($C_{20}H_{38}N_2O_2Na$): 361.28350 (calculated: 361.2831).

<u>Example 13:</u> (*S*)-3-(decyloxycarbonyl)amino-caprolactam:

(*S,S*)-3-amino-caprolactam hydro-pyrrolidine-5-carboxylate (2 mmol) and Na_2CO_3 (6 mmol) in water (25 ml) were added to a solution of decyl chloroformate (2 mmol) in dichloromethane (25 ml) at ambient temperature and the reaction mixture was stirred for 2 hours. The organic layer was then separated and the aqueous phase was extracted with additional dichloromethane (2 × 25 ml). The combined organic layers were dried over Na_2CO_3 and reduced *in vacuo*. The residue was purified by silica column chromatography (eluent: EtOAc to 9:1 EtOAc:MeOH) to give the title compound (459 mg; 74%).

Melting point: 40-41 °C.

$[\alpha]_D^{25}$ (c = 1, $CHCl_3$) = +31.4.

IR: ν_{max} (cm^{-1}): 3352, 3300 (NH), 1682, 1657, 1637 (CO), 1513 (NH).

^{1}H NMR (δ_H, 500 MHz, $CDCl_3$): 6.86 (1H, br s, CH_2N*H*), 6.72 (1H, d, *J* 6 CHN*H*), 4.49 (1H, dd, *J* 11, 6, C*H*NH), 3.99 (2H, t, *J* 6, OCH_2), 3.26-3.14 (2H, m, CH_2NH), 2.04 (1H, br d, *J* 13.5, ring CH), 2.00-1.91 (1H, m, ring CH), 1.82-1.68 (2H, m, ring

CH), 1.55 (2H, br qn *J* 7.0, C*H*$_2$CH$_2$O), 1.48 (1H, br qd, *J* 14, 2.5, ring CH), 1.38-1.31 (1H, br m, ring CH), 1.29-1.17 (14H, m, (CH$_2$)$_7$) and 0.83 (3H, t, *J* 7, CH$_3$).

^{13}C NMR (δ_C, 125 MHz, CDCl$_3$): 175.8, 155.9 (CO), 65.0 (OCH$_2$), 53.5 (NHCHCO), 42.0 (NCH$_2$), 32.1, 31.8, 29.5 (×2), 29.2 (×2), 29.0, 28.8, 28.0, 25.8, 22.6 (CH$_2$) and 14.1 (CH$_3$).

m/z ($C_{17}H_{32}N_2O_3Na$): 335.23190 (calculated: 335.2311).

<u>Example 14:</u> (*S*)-(*E*)-3-(dodec-2-enoyl)amino-caprolactam:

(*S,S*)-3-amino-caprolactam hydro-pyrrolidine-5-carboxylate (2 mmol) and Na$_2$CO$_3$ (6 mmol) in water (25 ml) were added to a solution of dodec-2-enoyl chloride (2 mmol) in dichloromethane (25 ml) at ambient temperature and the reaction mixture was stirred for 2 hours. The organic layer was then separated and the aqueous phase was extracted with additional dichloromethane (2 × 25 ml). The combined organic layers were dried over Na$_2$CO$_3$ and reduced *in vacuo*. The residue was purified by silica column chromatography (eluent: EtOAc to 9:1 EtOAc:MeOH) to give the title compound (472 mg; 77%).

Melting point: 87-88 °C.

$[\alpha]_D^{25}$ (c = 1, CHCl$_3$) = +44.7.

IR: ν_{max} (cm^{-1}): 3382, 3331 (NH), 1660, 1616 (CO), 1520 (NH).

^{1}H NMR (δ_H, 500 MHz, CDCl$_3$): 6.94 (1H, d, *J* 5.5, CHN*H*), 6.84 (1H, br s, CH$_2$N*H*), 6.78 (1H, dt, *J* 15.5, 7, CH$_2$C*H*=CH), 5.80 (1H, d, *J* 15.5, CH$_2$CH=C*H*), 4.56 (1H, ddd, *J* 11, 6, 1.5, C*H*NH), 3.29-3.15 (2H, m, C*H*$_2$NH), 2.11 (2H, q, *J* 7, C*H*$_2$CH=CH), 2.07 (1H, br d, *J* 13.5, ring CH), 1.98-1.90 (1H, m, ring CH), 1.86-1.73 (2H, m, ring CH), 1.44 (1H, br qd, *J* 14, 2.5, ring CH), 1.41-1.29 (3H, br m, ring CH + C*H*$_2$CH$_2$CH=CH), 1.29-1.14 (12H, m, (CH$_2$)$_6$) and 0.82 (3H, t, *J* 6.5, CH$_3$).

^{13}C NMR (δ_C, 125 MHz, CDCl$_3$): 175.9, 165.0 (CO), 144.8, 123.5 (CH=CH), 52.0 (NHCHCO), 42.0 (NCH$_2$), 32.0, 31.8, 31.6, 29.4 (×2), 29.2, 29.1, 28.8, 28.2, 27.9, 22.6 (CH$_2$) and 14.1 (CH$_3$).

m/z ($C_{18}H_{32}N_2O_2Na$): 331.23570 (calculated: 331.2361).

<u>Example 15:</u> (*S*)-3-(dec-9-enylaminocarbonyl)amino-caprolactam:

(*S*,*S*)-3-amino-caprolactam hydro-pyrrolidine-5-carboxylate (2 mmol) and Na_2CO_3 (6 mmol) in water (25 ml) were added to a solution of dec-9-enyl isocyanate (2 mmol) in dichloromethane (25 ml) at ambient temperature and the reaction mixture was stirred for 2 hours. The organic layer was then separated and the aqueous phase was extracted with additional dichloromethane (2 × 25 ml). The combined organic layers were dried over Na_2CO_3 and reduced *in vacuo*. The residue was purified by silica column chromatography (eluent: EtOAc to 9:1 EtOAc:MeOH) to give the title compound (347 mg; 56%).

Melting point: 98-99 °C.

$[\alpha]_D^{25}$ (c = 1, $CHCl_3$) = +27.3.

IR: ν_{max} (cm^{-1}): 3365, 3327, 3276 (NH), 1619, (CO), 1551 (NH).

^{1}H NMR (δ_H, 500 MHz, $CDCl_3$): 6.64 (1H, br s, ring CH_2N*H*), 6.12 (1H, d, *J* 6 CHN*H*), 5.75 (1H, ddtd, *J* 17, 10, 6.5, 1.5, CH_2=C*H*), 5.21-5.12 (1H, br m, urea CH_2NH), 4.93 (1H, dq, *J* 17, 1.5, C*H*H=CH), 4.87 (1H, br d, *J* 10, CH*H*=CH), 4.49 (1H, dd, *J* 11, 6, NHC*H*CO), 3.25 (1H, ddd, *J* 15.5, 12, 4, ring CH_2N), 3.17 (1H, dt, *J* 14, 6, ring CH_2N), 3.11-3.02 (2H, m, urea NHCH_2), 2.05-1.87 (4H, br m, ring CH ×2 + CH_2CH=CH), 1.82-1.70 (2H, m, ring CH), 1.48-1.36 (3H, br m, chain C$H_2$$CH_2$NH, + ring CH), 1.36-1.27 (3H, m, ring CH + chain CH_2) and 1.27-1.17 (8H, m, chain $(CH_2)_4$).

^{13}C NMR (δ_C, 125 MHz, $CDCl_3$): 177.2, 157.6 (CO), 139.1, 114.1 (CH=CH), 52.7 (NHCHCO), 42.1, 40.3 (NCH_2), 33.7, 32.9, 30.3, 29.4, 29.3, 29.0, 28.8 (×2), 27.9 and 26.9 (CH_2).

m/z ($C_{17}H_{31}N_3O_2Na$): 332.23150 (calculated: 332.2314).

Example 16: (*S*)-3-(decylaminocarbonyl)amino-caprolactam:

(*S*,*S*)-3-amino-caprolactam hydro-pyrrolidine-5-carboxylate (2 mmol) and Na_2CO_3 (6 mmol) in water (25 ml) were added to a solution of decyl isocyanate (2 mmol) in dichloromethane (25 ml) at ambient temperature and the reaction mixture was stirred for 2 hours. The organic layer was then separated and the aqueous phase was extracted with additional dichloromethane (2 × 25 ml). The combined organic layers were dried over Na_2CO_3 and reduced *in vacuo*. The residue was purified by silica column chromatography (eluent: EtOAc to 9:1 EtOAc:MeOH) to give the title compound (401 mg, 64%).

Melting point: 97-98 °C.

$[\alpha]_D^{20}$ (c = 1, $CHCl_3$) = +27.7.

IR: ν_{max} (cm^{-1}): 3359, 3316 (NH), 1621, (CO), 1558 (NH).

^1H NMR (δ_H, 500 MHz, $CDCl_3$): 6.62 (1H, br s, ring CH_2NH), 6.09 (1H, d, J 6 CHNH), 5.16 (1H, br t, J 5, urea CH_2NH), 4.48 (1H, ddd, J 11, 6, 1, NHCHCO), 3.26 (1H, ddd, J 16, 11, 5, ring CH_2N), 3.17 (1H, dt, J 15, 7, ring CH_2N), 3.11-3.02 (2H, m, urea NHCH_2), 2.02 (1H, br d J 14, ring CH), 1.96-1.87 (1H, m, ring CH), 1.83-1.70 (2H, m, ring CH), 1.48-1.27 (4H, br m, ring CH ×2 + chain CH_2), 1.27-1.14 (14H, m, $(CH_2)_7$) and 0.82 (3H, t, J 7, CH_3).

^{13}C NMR (δ_C, 125 MHz, $CDCl_3$): 177.2, 157.6 (CO), 52.7 (NHCHCO), 42.1, 40.4 (NCH_2), 32.9, 31.8, 30.2, 29.6, 29.5, 29.4, 29.3, 28.8, 27.9, 26.9, 22.6 (CH_2) and 14.1.

m/z ($C_{17}H_{33}N_3O_2Na$): 334.24880 (calculated: 334.2470).

<u>EXAMPLE 17:</u> (S)-aminocaprolactam-Glycine-(L) Tryptophan:

<u>Pharmacological study of the products of the invention</u>

<u>Inhibition of MCP-1 induced leukocyte migration</u>

Assay principle

The biological activity of the compounds of the current invention may be demonstrated using any of a broad range of functional assays of leukocyte migration in vitro, including but not limited to Boyden chamber and related transwell migration assays, under-agarose migration assays and direct visualisation chambers such as the Dunn Chamber.

For example, to demonstrate the inhibition of leukocyte migration in response to chemokines (but not other chemoattractants) the 96-well format micro transwell assay system from Neuroprobe (Gaithersburg, MD, USA) has been used. In principle, this assay consists of two chambers separated by a porous membrane. The chemoattractant is placed in the lower compartment and the cells are placed in the upper compartment. After incubation for a period at 37°C the cells move towards the chemoattractant, and the number of cells in the lower compartment is proportional to the chemoattractant activity (relative to a series of controls).

This assay can be used with a range of different leukocyte populations. For example, freshly prepared human peripheral blood leukocytes may used. Alternatively, leukocyte subsets may be prepared, including polymorphonuclear cells or lymphocytes or monocytes using methods well known to those skilled in the art such as density gradient centrifugation or magnetic bead separations. Alternatively, immortal cell lines which have been extensively validated as models of human peripheral blood leukocytes may be used, including, but not limited to THP-1 cells as a model of monocytes or Jurkat cells as model of naïve T cells.

Although a range of conditions for the assay are acceptible to demonstrate the inhibition of chemokine-induced leukocyte migration, a specific example is hereby provided.

Materials

The transwell migration systems are manufactured by Neuroprobe, Gaithersburg, MD, USA.

The plates used are ChemoTx plates (Neuroprobe 101-8) and 30 µl clear plates (Neuroprobe MP30).

Geys' Balanced Salt Solution is purchased from Sigma (Sigma G-9779).

Fatty acid-free BSA is purchased from Sigma (Sigma A-8806).

MTT, i.e. 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide, is purchased from Sigma (Sigma M-5655).

RPMI-1640 without phenol red is purchased from Sigma (Sigma R-8755).

The THP-1 cell line (European Cell culture Collection) were used as the leukocyte cell population.

Test protocol

The following procedure is used for testing the invention compounds for MCP-1 induced leukocyte migration:

First, the cell suspension to be placed in the upper compartment is prepared. The THP-1 cells are pelleted by centrifugation (770 x g; 4 mins) and washed with Geys Balanced Salt Solution with 1mg/ml BSA (GBSS + BSA). This wash is then repeated, and the cells repelleted before being resuspended in a small volume of GBSS + BSA for counting, for example using a standard haemocytometer.

The volume of GBSS + BSA is then adjusted depending on the number of cells present so that the cells are at final density of 4.45 x 10^6 cells per ml of GBSS + BSA. This ensures that there are 100,000 THP-1 cells in each 25µl of the solution that will be placed in the upper chamber of the plate.

To test a single compound for its ability to inhibit MCP-1 induced migration, it is necessary to prepare two lots of cells. The suspension of THP-1 cells at 4.45 x 10^6 cells/ml is divided into two pots. To one pot the inhibitor under test is added at an appropriate final concentration, in an appropriate vehicle (for example at 1µM in not more than 1% DMSO). To the second pot an equal volume of GBSS + BSA plus vehicle as appropriate (e.g. not more than 1% DMSO) is added to act as a control.

Next, the chemoattractant solution to be placed in the lower compartment is prepared. MCP-1 is diluted in GBSS + BSA to give a final concentration of 25 ng/ml. This is divided into two pots, as for the cell suspension. To one pot, the test compound is added to the same final concentration as was added to the cell suspension, while to the other pot an equal volume of GBSS + BSA plus vehicle as appropriate (e.g. not more than 1% DMSO) is added.

Note that the volume of liquid that needs to be added to make the addition of the text compound needs to be taken into account, when establishing the final concentration of MCP-1 in the solution for the lower compartment and the final concentration of cells in the upper compartment.

Once the chemoattractant solutions for the lower wells and cell solutios for the upper chambers have been prepared, the migration chamber should be assembled. Place 29 µl of the appropriate chemoattractant solution into the lower well of the chamber. Assays should be performed with at least triplicate determinations of each condition. Once all the lower chambers have been filled, apply the prous membrane to the chamber in accordance with the manufacturer's instructions. Finally, apply 25 µl of the appropriate cell solution to each upper chamber. A plastic lid is placed over the entire apparatus to prevent evaporation.

The assembled chamber is incubated at 37 °C, 5% CO_2, for 2 hours. A suspension of cells in GBSS + BSA is also incubated under identical conditions in a tube: these cells will be used to construct a standard curve for determining the number of cells that have migrated to the lower chamber under each condition.

At the end of the incubation, the liquid cell suspension is gently removed from the upper chamber, and 20µl of ice-cold 20mM EDTA in PBS is added to the upper

chamber, and the apparatus is incubated at 4°C for 15 mins. This procedure causes any cells adhering to the underside of the membrane to fall into the lower chamber.

After this incubation the filter is carefully flushed with GBSS + BSA to wash off the EDTA, and then the filter is removed.

The number of cells migrated into the lower chamber under each condition can then be determined by a number of methods, including direct counting, labelling with fluorescent or radioactive markers or through the use of a vital dye. Typically, we utilise the vital dye MTT. 3 µl of stock MTT solution are added to each well, and then the plate is incubated at 37 °C for 1-2 hours during which time dehydrogenase enzymes within the cells convert the soluble MTT to an insoluble blue formazan product that can be quantified spectrophotometrically.

In parallel, an 8-point standard curve is set up. Starting with the number of cells added to each upper chamber (100,000) and going down in 2-fold serial dilutions in GBSS + BSA, the cells are added to a plate in 25 µl, with 3 µl of MTT stock solution added. The standard curve plate is incubated along side the migration plate.

At the end of this incubation, the liquid is carefully removed from the lower chambers, taking care not to disturb the precipitated formazan product. After allowing to air dry briefly, 20µl of DMSO is added to each lower chamber to solubilise the blue dye, and absorbance at 595nm is determined using a 96-well plate reader. The absorbance of each well is then interpolated to the standard curve to estimate the number of cells in each lower chamber.

The MCP-1 stimulated migration is determined by subtracting the average number of cells that reached the lower compartment in wells where no MCP-1 was added from the average number of cells that reached the lower compartment where MCP-1 was present at 25ng/ml.

The impact of the test substance is calculated by comparing the MCP-1-induced migration which occurred in the presence or absence of various concentrations of the test substance. Typically, the inhibition of migration is expressed as a percentage of the total MCP-1 induced migration which was blocked by the presence of the compound. For most compounds, a dose-response graph is constructed by determining the inhibition of MCP-1 induced migration which occurs at a range of different compound concentrations (typically ranging from 1nM to 1µM or higher in the case of poorly active compounds). The inhibitory activity of each compound is then expressed as the

concentration of compound required to reduce the MCP-1-induced migration by 50% (the ED_{50} concentration).

Results

The compounds of examples 1 to 7 and 9 to 14 were tested and were shown to have an ED_{50} of 100 nM or less in this test.

Enantioselectivity

The (S)- and (R)- enantiomers of two different members of the aminocaprolactam series were synthesised to determine whether the biological activity showed enantioselectivity.

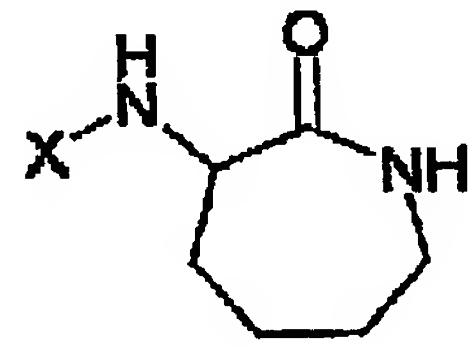
The comparison was made between the compounds of examples 1 and 7, and between the compounds of examples 10 and 11.

The dose-response curves for each of the four compounds as inhibitors of MCP-1 induced THP-1 cell migration were determined using the transwell migration assay and are shown in Figure 1. In both cases, the (S)-enantiomer was significantly (10-50 fold) more active than the (R)-enantiomer.

These data, for two example members of the aminocaprolactam series, demonstrate that for the application of the compounds of the present invention as anti-inflammatory agents in vivo it is preferable to use the pure (S)-enantiomer of the compound, rather than the racemic mixture of the two enantiomers or the pure (R)-enantiomer.

Claims

1. Use of a compound of general formula (I) or a pharmaceutically acceptable salt thereof, for the preparation of a medicament intended to treat an inflammatory disorder:



(I)

wherein

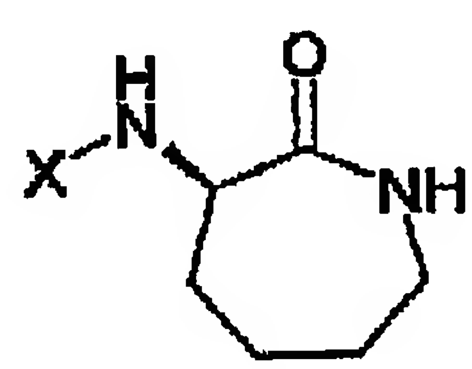
X is -CO-R^1 or -SO_2-R^2,

R^1 is an alkyl, haloalkyl, alkoxy, haloalkoxy, alkenyl, alkynyl or alkylamino radical of 4 to 20 carbon atoms (for example of 5 to 20 carbon atoms, of 8 to 20 carbon atoms, of 9 to 20 carbon atoms, of 10 to 18 carbon atoms, of 12 to 18 carbon atoms, of 13 to 18 carbon atoms, of 14 to 18 carbon atoms, of 13 to 17 carbon atoms.); and

R^2 is an alkyl radical of 4 to 20 carbon atoms (for example of 5 to 20 carbon atoms, of 8 to 20 carbon atoms, of 9 to 20 carbon atoms, of 10 to 18 carbon atoms, of 12 to 18 carbon atoms, of 13 to 18 carbon atoms, of 14 to 18 carbon atoms, and of 13 to 17 carbon atoms); or

alternatively R^1 and R^2 are selected independently from a peptido radical having from 1 to 4 peptidic moieties linked together by peptide bonds.

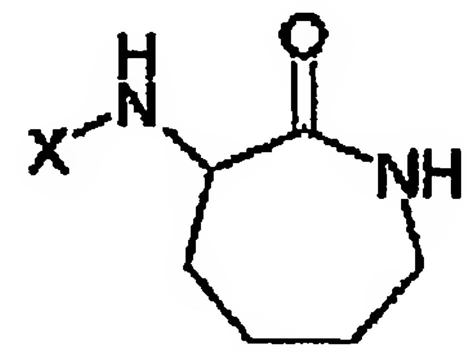
2. Use of a compound of formula (I') or a pharmaceutically acceptable salt thereof, for the preparation of a medicament intended to treat an inflammatory disorder:



(I')

wherein X has the same meaning as above.

3. A pharmaceutical composition comprising, as active ingredient, a compound of formula (I) or a pharmaceutically acceptable salt thereof, and at least one pharmaceutically acceptable excipient and/or carrier:



(I)

wherein

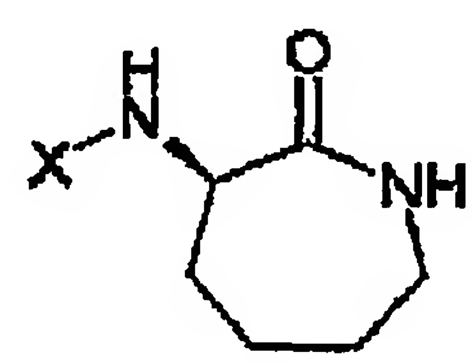
X is $-CO-R^1$ or $-SO_2-R^2$,

R^1 is an alkyl, haloalkyl, alkoxy, haloalkoxy, alkenyl, alkynyl or alkylamino radical of 4 to 20 carbon atoms (for example of 5 to 20 carbon atoms, of 8 to 20 carbon atoms, of 9 to 20 carbon atoms, of 10 to 18 carbon atoms, of 12 to 18 carbon atoms, of 13 to 18 carbon atoms, of 14 to 18 carbon atoms, of 13 to 17 carbon atoms.); and

R^2 is an alkyl radical of 4 to 20 carbon atoms (for example of 5 to 20 carbon atoms, of 8 to 20 carbon atoms, of 9 to 20 carbon atoms, of 10 to 18 carbon atoms, of 12 to 18 carbon atoms, of 13 to 18 carbon atoms, of 14 to 18 carbon atoms, and of 13 to 17 carbon atoms); or

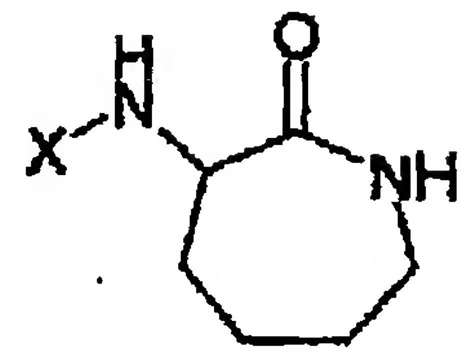
alternatively R^1 and R^2 may be selected independently from a peptido radical having from 1 to 4 peptidic moieties linked together by peptide bonds (for example a peptido radical of 1 to 4 amino acid residues).

4. A pharmaceutically acceptable composition comprising active ingredient, a compound of formula (I') or a pharmaceutically acceptable salt thereof, and at least one pharmaceutically acceptable excipient and/or carrier:



(I')

5. A compound of general formula (I):



(I)

wherein

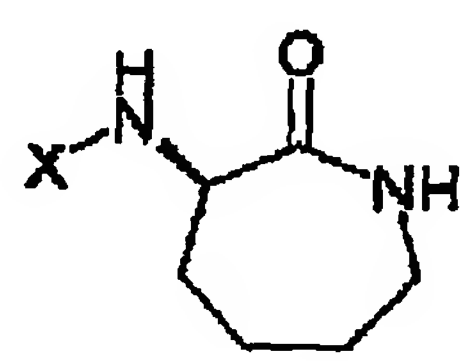
X is -CO-R^1 or -SO_2-R^2,

R^1 is an alkyl, haloalkyl, alkoxy, haloalkoxy, alkenyl, alkynyl or alkylamino radical of 4 to 20 carbon atoms (for example of 5 to 20 carbon atoms, of 8 to 20 carbon atoms, of 9 to 20 carbon atoms, of 10 to 18 carbon atoms, of 12 to 18 carbon atoms, of 13 to 18 carbon atoms, of 14 to 18 carbon atoms, of 13 to 17 carbon atoms.); and

R^2 is an alkyl radical of 4 to 20 carbon atoms (for example of 5 to 20 carbon atoms, of 8 to 20 carbon atoms, of 9 to 20 carbon atoms, of 10 to 18 carbon atoms, of 12 to 18 carbon atoms, of 13 to 18 carbon atoms, of 14 to 18 carbon atoms, and of 13 to 17 carbon atoms); or

alternatively R^1 and R^2 are selected independently from a peptido radical having from 1 to 4 peptidic moieties linked together by peptide bonds.

6. A compound of general formula (I'):



(I')

wherein X has the same meaning as above.

7. Compounds, compositions and uses of the compounds of general formula (I) or (I'), or their pharmaceutically acceptable salts, according to any preceding claim, wherein the alkyl, haloalkyl, alkoxy, haloalkoxy, alkenyl, alkynyl or alkylamino part of the R^1

radical is either linear or is branched but contains a linear chain of at least 8 or 10 carbon atoms.

8. A use according to claim 1 or a pharmaceutical composition according to claim 3, or a compound according to claim 5, wherein the compound is selected from the group consisting of:

- (*S*)-3-hexadecanoylamino-caprolactam;

- (*S*)-3-undecanoylamino-caprolactam;

- (S)-3-(undec-10-enoyl)amino-caprolactam;

- (*S*)-3-(undec-10-ynoyl)amino-caprolactam;

- (*S*)-3-dodecanoylamino-caprolactam;

- (*S*)-3-tetradecanoylamino-caprolactam;

- (*R*)-3-hexadecanoylamino-caprolactam;

- (*S*)-3-octadecanoylamino-caprolactam;

- (*S*)-(*Z*)-3-(hexadec-9-enoyl)amino-caprolactam;

- (*S*)-(*Z*)-3-(octadec-9-enoyl)amino-caprolactam;

- (*R*)-(*Z*)-3-(octadec-9-enoyl)amino-caprolactam;

- (*S*)-3-(2',2'-dimethyl-dodecanoyl)amino-caprolactam;

- (*S*)-3-(decyloxycarbonyl)amino-caprolactam;

- (*S*)-(*E*)-3-(dodec-2-enoyl)amino-caprolactam;

- (*S*)-3-(dec-9-enylaminocarbonyl)amino-caprolactam;

- (*S*)-3-(decylaminocarbonyl)amino-caprolactam;

and pharmaceutically acceptable salts thereof.

9. A use according to claim 1 or pharmaceutical composition according to claim 3, or a compound according to claim 5 wherein the compound is selected from the group

consisting of: (S)-3-hexadecanoylamino-caprolactam, (*S*)-3-(2',2'-dimethyl-dodecanoyl)amino-caprolactam and pharmaceutically acceptable salts thereof.

10. Use of a compound of formula (I) or (I') according to one of claims 1, 2, 8 and 9 wherein the inflammatory disorder is selected from the group consisting of autoimmune diseases, vascular disorders, viral infection or replication, asthma, osteoporosis (low bone mineral density), tumor growth, rheumatoid arthritis, organ transplant rejection and/or delayed graft or organ function, a disorder characterised by an elevated TNF-α level, psoriasis, skin wounds, disorders caused by intracellular parasites, allergies, Alzheimer's disease, antigen induced recall response, immune response suppression, multiple sclerosis, ALS, fibrosis, and formation of adhesions.

11. A method of treatment, amelioration or prophylaxis of the symptoms of an inflammatory disease (including an adverse inflammatory reaction to any agent) by the administration to a patient of an anti-inflammatory amount of a compound, composition or medicament as claimed in any of claims 1 to 9.

12. Compounds, compositions, and uses of the compounds of general formula (I) or (I'), or their pharmaceutically acceptable salts, or a method of treatment according to any preceding claim wherein the substituent R^1 is not a straight chain alkyl group.

13. Compounds, compositions, and uses of the compounds of general formula (I) or (I'), or their pharmaceutically acceptable salts, or a method of treatment according to any preceding claim wherein the substituent R^1 is a branched chain alkyl group.

14. Compounds, compositions, and uses of the compounds of general formula (I) or (I'), or their pharmaceutically acceptable salts, or a method of treatment according to any preceding claim wherein the substituent R^1 is not an alkyl group.

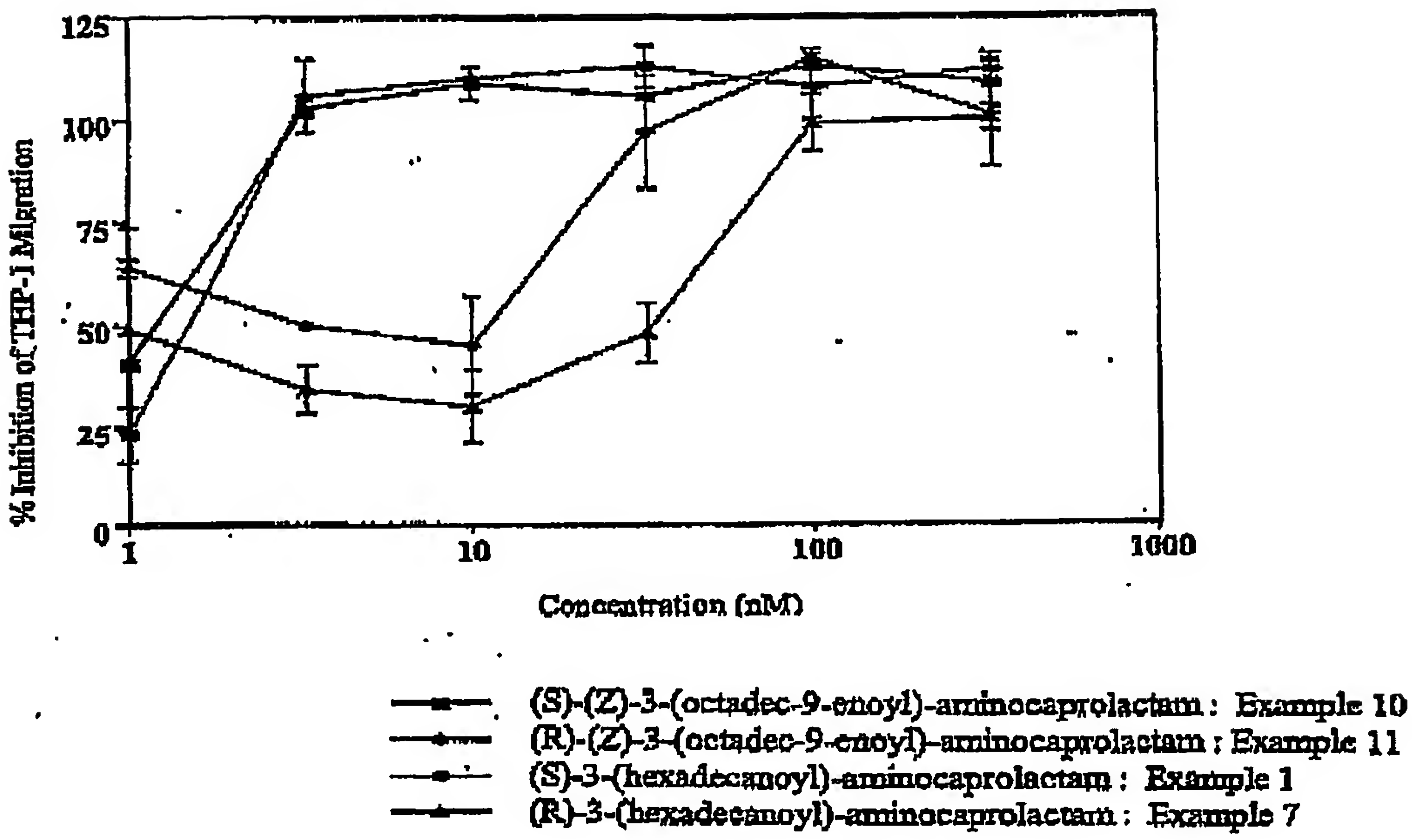

125
100
75
50
25
0
1
10
100
1000
% Inhibition of THP-1 Migration
Concentration (nM)
(S)-(Z)-3-(octadec-9-enoyl)-aminocaprolactam : Example 10
(R)-(Z)-3-(octadec-9-enoyl)-aminocaprolactam : Example 11
(S)-3-(hexadecanoyl)-aminocaprolactam : Example 1
(R)-3-(hexadecanoyl)-aminocaprolactam : Example 7

FIGURE 1

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